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New acid BisGMA analogs for dental adhesive applications with antimicrobial activity

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ABSTRACT

Objective. To achieve bisphenol A glycerolate dimethacrylate (BisGMA) analogs with reduced viscosity to be used in the formulation of dental adhesives containing biocidal components.
Methods. A series of low-viscosity BisGMA derivatives (η: 39–12 Pa s) modified with 30, 60 and, respectively 80 mol% carboxylic acid units were synthesized and characterized. Hydrogen bonding interactions in our monomers, the photopolymerization behavior and implicitly the conversion degree (DC) for some experimental adhesive formulations containing acid-modified BisGMA, commercial BisGMA (only in F1–F3), triethyleneglycol dimethacrylate and 2-hydroxyethyl methacrylate were examined by FTIR spectroscopy. The water effects on the photocrosslinked networks together with the flexural strength/modulus were also investigated. The adhesive penetration into the dentin surface was surveyed by SEM analysis, and the antimicrobial activity triggered by the incorporation of 0.5 wt% $AgNO_3$, 10 wt% zinc methacrylate or 1 wt% triclosan methacrylate in selected adhesive formulations on the growth of *Streptococcus mutans* and *Candida albicans* strains was evidenced.
Results. The contribution of the hydrogen bonding interactions was found to be lower in BisGMA derivatives than in non-modified BisGMA, and the DC varied between 56.5 (F6) and 83.7% (F1) compared with a control formulation based on BisGMA:TEGDMA (DC = 58.2%). The flexural strength and flexural modulus varied in the range 33.7 MPa (F6)–54.4 MPa (F8) MPa and 0.64 (F6)–1.43 (F8) GPa, respectively. SEM observation of adhesive-dentin interface revealed the formation of resin tags for the carboxyl-containing adhesive, while for the control adhesive they are hardly formed. Also, the microorganism development was inhibited, the proposed materials displaying antimicrobial activity.
Significance. The experimental formulations based on carboxyl-functionalized BisGMA exhibit a similar or even improved behavior over control sample, suggesting their potential applicability as antimicrobial dental adhesives.

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1. Introduction

Depending on the clinical approach, the contemporary dental adhesives were classified as either etch-and-rinse or self-etch systems, although the main goal is the achieving of a strong and durable bonding between the restorative composite and the hard dental tissue (dentin or enamel) through the infiltration of the fluid adhesive into the tooth surfaces [1,2]. However, besides the application procedure, the attaining of an efficient and stable adhesive bonding is strongly influenced by several factors such as the chemical structure of the functional monomers/composition, interactions between monomers, hydrophilic/hydrophobic character, evolution of the photopolymerization process, and so on [3,4]. The components included into the adhesive systems are generally based on monomers bearing both photopolymerizable and acidic groups (carboxylic, phosphoric or phosphonic acids) mixed with crosslinking dimethacrylates, solvents (ethanol, water, acetone), polymerization initiators, and other monofunctional additives [5–8]. The majority of acidic monomers reported in literature are methacrylate or acrylamide type, functionalized with phosphate, phosphonate or carboxyl moieties [9–11] in order to impart the desired features to the adhesive materials. In addition, the dental adhesives contain cross-linking dimethacrylates [*e.g.*, 2,2-bis[4-(2-hydroxy-3-methacryloyloxypropoxy)-phenyl] propane (BisGMA), triethyleneglycol dimethacrylate (TEGDMA), 1,6-bis-[2-methacryloyloxyethoxycarbonylamino]-2,4,4-trimethylhexane (UDMA), or glycerol dimethacrylate (GDMA)], that are essential in the formation of adhesive polymer networks. They favorably increased the polymerization rate through a "gel-effect" leading to improved mechanical strength of the adhesive layer and stability of the adhesive interface over time, in conjunction with a decreased swelling degree [2,12]. Among these, the most frequently used not only in adhesive systems but also in resin composites is the well-known crosslinking monomer BisGMA (Bowen's resin), due to its low polymerization shrinkage, high esthetic quality, and superior mechanical strength. Still, the main drawback of BisGMA monomer is related to its high viscosity (in the range of 500–1200 Pa s), attributed to the intermolecular hydrogen bonding between the hydroxyl groups present in the monomer structure [13]. To overcome this disadvantage, various strategies have been proposed. In most cases the combination with lower-molecular-weight and low-viscosity monomers (*e.g.*, TEGDMA) was preferred, because it reduces the viscosity of formulations but increases the curing shrinkage, water uptake and depreciates the mechanical characteristics of the final materials [14]. Another attractive approach refers to the achievement of BisGMA derivatives with lower viscosities, through the chemical modification of hydroxyl groups with alkyl-urethane, alkoxy, urethane-methacrylate or silyl sequences that decrease the hydrogen bonding extent [15–19] and consequently, diminish the amount of diluent monomer required of a workable dental mix. Moreover, up to now, for adhesive applications only a phosphoric ester of BisGMA obtained by the treatment of BisGMA with phosphorus oxychloride was reported in the literature [20].

On the other hand, the self-etching adhesives incorporating acidic monomers with lower pH in formulation may present a limited antibacterial effect to 24 or 48 h [21], and the addition of selected biocidal agents (*e.g.*, chlorohexidine, fluoride, silver particles) in the matrix provide antibacterial-agent releasing materials which impede the caries occurrence. Since in such systems the physical properties were negatively affected by the release of the biocide from the polymeric network without neglecting its toxic effect and uncontrolled release kinetics, the development of non-antibacterial agent releasing materials (*e.g.*, quaternary ammonium monomers) capable to generate long-term antibacterial activity [22,23] remains a field of active research. As reported by Wang et al. [24] the presence of antibacterial monomers in adhesive compositions could be advantageously because their qualities to reduce biofilm accumulation preventing the evolution of dental caries and improving the longevity of materials.

On this line, the present study describes the synthesis, characterization, and photopolymerization behavior of new acid BisGMA derivatives prepared through the functionalization of hydroxyl units from the pristine BisGMA with carboxyl sequences introduced in variable proportions (from 30 to 80 mol%) by means of succinic anhydride. The proposed monomers are intended to be used in adhesive formulations along with other photopolymerizable commercial monomers commonly encountered in such systems, in order to evaluate their influence on the specific properties for this kind of dental materials including the formation of photopolymerized resin tags. Due to the widespread susceptibility to bacteria and fungi colonization into the oral environment that may cause recurrent caries, some antibacterial agents (silver nanoparticles, zinc methacrylate or triclosan methacrylate) were included in dental adhesive resins to impart antimicrobial activity to the resulting adhesives [25–27]. Furthermore, it is expected that the covalent immobilization of the monomer units with potential antimicrobial functions in the polymer backbone to inhibit bacterial growth by contact mechanism allowing an improved control of the antibacterial activity and a long-lasting effect owing to the non-leaching of them from the photocrosslinked matrix [28,29].

2. Materials and methods

2.1. Materials

Bisphenol A glycerolate dimethacrylate (BisGMA), lithium hydride, succinic anhydride, camphorquinone (CQ), 4-(dimethylamino) phenylacetic acid (DMPheAA), silver nitrate ($AgNO_3$) and zinc methacrylate were purchased from Sigma Aldrich Chemical Co. and used without further purification. The commercial monomers used in this study are 2-hydroxyethyl methacrylate (HEMA) and triethyleneglycol dimethacrylate (TEGDMA) (Sigma–Aldrich Chemical Co.).

2.2. Synthesis of the BisGMA derivatives modified with carboxyl groups

The synthesis conditions for the obtaining of BisGMA derivatives modified with carboxyl groups (BisGMA-COOH1,